NIH-FDA IIG

National Institutes of Health // Food and Drug Administration // Immunology Interest Group

NEWSLETTER

JULY 2023

PUBLICATIONS

Neutrophil extracellular traps and extracellular histones potentiate IL-17 inflammation in periodontitis

Kim TS, Silva LM, Theofilou VI, Greenwell-Wild T, Li L, Williams DW, Ikeuchi T, Brenchley L; NIDCD/NIDCR Genomics and Computational Biology Core; Bugge TH, Diaz PI, Kaplan MJ, Carmona-Rivera C, Moutsopoulos NM.
J Exp Med. 2023 Sep 4;220(9):e20221751.
PMID: 37261457 PMCID: PMC10236943 (available on 2023-12-01) DOI: 10.1084/jem.20221751

Our studies provide evidence for the role of neutrophil extracellular traps and extracellular histones as early disease triggers of pathogenic oral mucosal inflammation in the disease periodontitis and support cross-regulation of neutrophil and IL-17 immunity in disease pathogenesis.

Emerging functions of thrombospondin-1 in immunity

Kaur S, Roberts DD.
Semin Cell Dev Biol. 2023 May 29;S1084-9521(23)00117-9.
PMID: 37258315 DOI: 10.1016/j.semcdb.2023.05.008

Thrombospondin-1 is a matricellular protein that regulates innate and adaptive immune cells by interactions with several cell surface receptors including CD47 and by its ability to directly activate latent TGF. Dysregulation of thrombospondin-1 expression contributes to altered immune function in several autoimmune diseases, diseases of aging, and cancer.

Virulence differences of mpox (monkeypox) virus clades I, IIa, and IIb.1 in a small animal model

Americo JL, Earl PL, Moss B.
Proc Natl Acad Sci USA. 2023 Feb 21;120(8):e2220415120.
PMID: 36787354 PMCID: PMC9974501 (available on 2023-08-14) DOI: 10.1073/pnas.2220415120

Genome sequencing has revealed differences between the current mpox virus outbreak strains, classified as clade IIb, and the prior clade IIa and clade I viruses, but whether these differences contribute to virulence or transmission has not been determined. We demonstrate that the wild-derived inbred castaneous mouse provides an exceptional animal model for investigating clade differences in mpox virus virulence and show that the order is clade I > clade IIa > clade IIb.1. The greatly reduced replication of the clade IIb.1 major outbreak strain in mice and absence of lethality at 100 times the lethal dose of a closely related clade IIa virus, despite similar multiplication in cell culture, suggest that clade IIb is evolving diminished virulence or adapting to other species.

C5a-licensed phagocytes drive sterilizing immunity during systemic fungal infection

Desai JV, Kumar D, Freiwald T, Chauss D, Johnson MD, Abers MS, Steinbrink JM, Perfect JR, Alexander B, Matzaraki V, Snarr BD, Zarakas MA, Oikonomou V, Silva LM, Shivarathri R, Beltran E, Demontel LN, Wang L, Lim JK, Launder D, Conti HR, Swamydas M, McClain MT, Moutsopoulos NM, Kazemian M, Netea MG, Kumar V, Köhl J, Kemper C, Afzali B, Lionakis MS.
Cell. 2023 Jun 22;186(13):2802-2822.e22.
PMID: 37220746 PMCID: PMC10330337 (available on 2024-06-22) DOI: 10.1016/j.cell.2023.04.031

In this work, we found that transcriptional induction of a complement module predicts human candidemia and that impaired complement activation independently correlates with poor outcomes in candidemic patients. Mechanistically, C5 produced both in the liver and by phagocytes locally in fungal-infected tissue promotes antifungal protection via stimulating C5aR1-dependent phagocyte survival and effector functions. Collectively, these findings demonstrate that intracellular complement contributes to antimicrobial host defense and explain why candidiasis develops in patients after C5 inhibition therapy.

Lipids regulate peripheral serotonin release via gut CD1d

Luo J, Chen Z, Castellano D, Bao B, Han W, Li J, Kim G, An D, Lu W, Wu C.
Immunity. 2023 Jul 11;56(7):1533-1547.e7. doi: 10.1016/j.immuni.2023.06.001.
PMID: 37354904 DOI: 10.1016/j.immuni.2023.06.001

The crosstalk between the immune and neuroendocrine systems is critical for intestinal homeostasis and gut-brain communications. We found that lipid-mediated engagement of invariant natural killer T (iNKT) cells with enterochromaffin (EC) cells, a subset of intestinal epithelial cells, promoted peripheral serotonin (5-HT) release via a CD1d-dependent manner, regulating gut motility and hemostasis.

Cathepsin W restrains peripheral regulatory T cells for mucosal immune quiescence

Li J, Chen Z, Kim G, Luo J, Hori S, Wu C.
Sci Adv. 2023 Jul 14;9(28):eadf3924.
PMID: 37436991 PMCID: PMC10337914 DOI: 10.1126/sciadv.adf3924

Peripheral regulatory T (pTreg) cells are a key T cell lineage for mucosal immune tolerance and anti-inflammatory responses. We found that Cathepsin W (CTSW), a cysteine proteinase highly induced in pTreg cells is essential in restraining pTreg cell differentiation for mucosal immune quiescence

Cxxc finger protein 1 maintains homeostasis and function of intestinal group 3 innate lymphoid cells with aging

Shen X, Gao X, Luo Y, Xu Q, Fan Y, Hong S, Huang Z, Liu X, Wang Q, Chen Z, Wang D, Lu L, Wu C, Liang H, Wang L.
Nat Aging. 2023 Jul 10.
PMID: 37429951 DOI: 10.1038/s43587-023-00453-7

Group 3 innate lymphoid cells (ILC3s) constitute a heterogeneous cell population that plays pivotal roles in intestinal immunity. We found that ILC3s in aged mice exhibited dysregulated homeostasis and function mediated by Cxxc finger protein 1 (Cxxc1), a key subunit of H3K4 methyltransferase, leading to bacterial and fungal infection susceptibility.

Murine allogeneic CAR T cells integrated before or early after posttransplant cyclophosphamide exert antitumor effects

Patterson MT, Khan SM, Nunes NS, Fletcher RE, Bian J, Hadjis AD, Eckhaus MA, Mendu SK, de Paula Pohl A, Venzon DJ, Choo-Wosoba H, Ishii K, Qin H, Fry TJ, Cam M, Kanakry CG.
Blood. 2023 Feb 9;141(6):659-672.
PMID: 36201744 PMCID: PMC9979711 DOI: 10.1182/blood.2022016660

In this preclinical murine hematopoietic cell transplant model, we have shown that engineered cell therapies such as anti-CD19 CAR-T cells as used here, can be integrated in the early post-allogeneic hematopoietic cell transplant setting using post-transplantation cyclophosphamide and exert an anti-tumor effect without aggravating graft-versus-host disease or worsening inflammation ongoing from the allogeneic response. This approach, if successful in clinical translation, would combine engineered cellular therapy and polyclonal alloreactive T-cell responses to hopefully reduce the risk of relapse in patients with high-risk hematologic malignancies, while decreasing the duration of treatment and allowing CAR-T cells to persist post-transplant.

The role of transcription factors in shaping regulatory T cell identity

Trujillo-Ochoa JL, Kazemian M, Afzali B.
Nat Rev Immunol. 2023 Jun 19.
PMID: 37336954 DOI: 10.1038/s41577-023-00893-7

Only a small fraction of Treg cell-associated genes are directly bound by FOXP3, and FOXP3 alone is insufficient to fully specify the Treg cell programme, indicating a role for other accessory transcription factors operating upstream, downstream and/or concurrently with FOXP3 to direct Treg cell specification and specialized functions. In this Review, we discuss the emerging roles of accessory transcription factors in controlling Treg cell identity, specifically focussing on members of the basic helix-loop-helix family (AHR), basic leucine zipper family (BACH2, NFIL3 and BATF), CUT homeobox family (SATB1), zinc-finger domain family (BLIMP1, Ikaros and BCL-11B) and interferon regulatory factor family (IRF4), as well as lineage-defining transcription factors (T-bet, GATA3, RORt and BCL-6).

Continued>>

Exploiting an Interleukin-15 Heterodimeric Agonist (N803) for Effective Immunotherapy of Solid Malignancies

Lui G, Minnar CM, Soon-Shiong P, Schlom J, Gameiro SR.
Cells. 2023 Jun 12;12(12):1611.
PMID: 37371081 PMCID: PMC10297013 DOI: 10.3390/cells12121611

N803 is a novel and potent Th1-inducing immunocytokine that promotes significant immune activation, proliferation, and cytolytic capacity of NK cells and CD8+ T cells. This review reports on the mechanisms of action of N803 as well as the results of preclinical and clinical studies using N803 in a combinatorial regimen, which strongly support its continued clinical development.

Pre-existing autoimmunity is associated with increased severity of COVID-19: A retrospective cohort study using data from the National COVID Cohort Collaborative (N3C)

Yadaw AS, Sahner DK, Sidky H, Afzali B, Hotaling N, Pfaff ER, Mathé EA; N3C consortium.
Clin Infect Dis. 2023 May 19:ciad294.
PMID: 37207367 DOI: 10.1093/cid/ciad294

Identifying individuals with a higher risk of developing severe COVID-19 outcomes will inform targeted or more intensive clinical monitoring and management. To date, there is mixed evidence regarding the impact of pre-existing autoimmune disease (AID) diagnosis and/or immunosuppressant (IS) exposure on developing severe COVID-19 outcomes. A retrospective cohort of adults diagnosed with COVID-19 was created in the National COVID Cohort Collaborative enclave (n= 2,453,799 adults diagnosed with COVID-19). Two outcomes, life-threatening disease, and hospitalization were evaluated by using logistic regression models with and without adjustment for demographics and comorbidities. The findings indicate that patients with pre-existing AID, exposure to IS, or both are more likely to have a life-threatening disease or hospitalization. These patients may thus require tailored monitoring and preventative measures to minimize negative consequences of COVID-19.

Multilevel human secondary lymphoid immune system compartmentalization revealed by complementary imaging approaches

Oyler BL, Valencia-Dávila JA, Moysi E, Molyvdas A, Ioannidou K, March K, Ambrozak D, De Leval L, Fabozzi G, Woods AS, Koup RA, Petrovas C.
iScience. 2023 Jul 3;26(8):107261.
PMID: 37520703 PMCID: PMC10371825 DOI: 10.1016/j.isci.2023.107261

In situ tissue profiling methodologies are indispensable for the understanding of compartmentalization of lymphoid tissue immune reactions. Here, we developed and employed a multi-modal imaging pipeline, combined with flow cytometry and lipidomic profiling of sorted lymphocytes, to monitor compartmentalization at tissue, cellular, and molecular levels.

Transcription factor EGR2 controls homing and pathogenicity of TH17 cells in the central nervous system

Gao Y, Wang Y, Chauss D, Villarino AV, Link VM, Nagashima H, Spinner CA, Koparde VN, Bouladoux N, Abers MS, Break TJ, Chopp LB, Park JH, Zhu J, Wiest DL, Leonard WJ, Lionakis MS, O'Shea JJ, Afzali B, Belkaid Y, Lazarevic V.
Nat Immunol. 2023 Aug;24(8):1331-1344.
PMID: 37443284 DOI: 10.1038/s41590-023-01553-7

IL-17A-producing CD4+ T cells (TH17 cells) protect barrier tissues, facilitate wound healing, and regulate host–microbiome interactions. Yet, TH17 cells can be major drivers of immune-related diseases. How these functionally opposing processes are controlled in TH17 cells remains unclear. In this study, we identified the transcription factor EGR2 (early growth response 2) as a key determinant of TH17 cell pathogenicity. EGR2 was found to govern TH17 cell migration, regulate expression of pathogenicity-associated genes, and facilitate recruitment of other immune cells in the central nervous system (CNS).

Continued>>

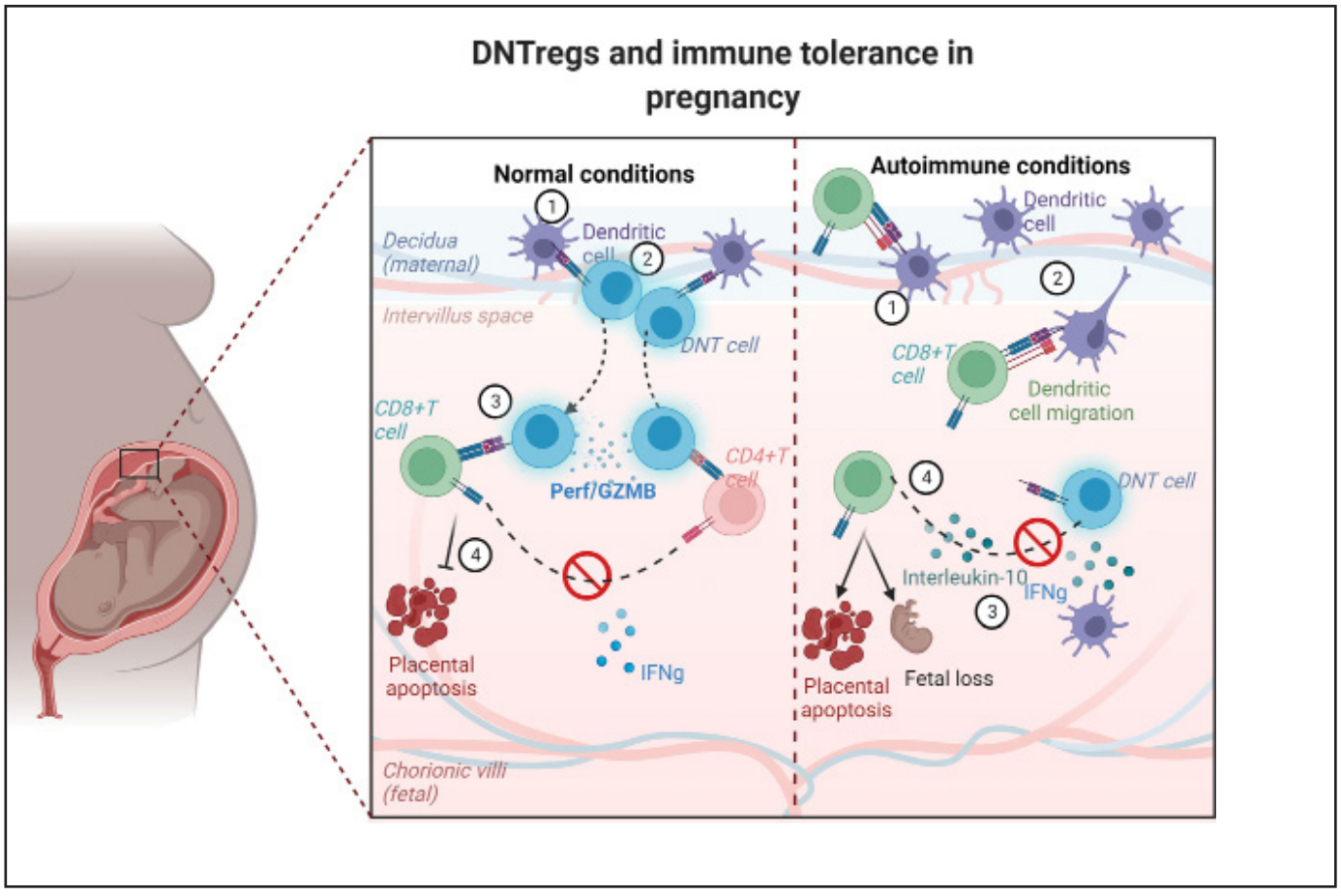
NCI Fellow Awarded the NIH Intramural Office of Autoimmune Diseases Research (IOADR) Fellowship

Dr. Enitome Bafor, a postdoctoral fellow in the Cancer Innovation Laboratory (CIL), NCI/CCR, led by Dr. Howard A. Young, has been awarded the NIH Intramural Office of Autoimmune Diseases Research (IOADR) Fellowship.

Dr. Bafor's research studies responses of the unconventional double negative T cells within the ovary and uterus, focusing on harnessing these cells to develop new immunotherapies against autoimmunity and cancer within the reproductive tract. She is utilizing a mouse model developed by the Young lab with chronic IFN-expression as a key model for her research.

Congratulations!

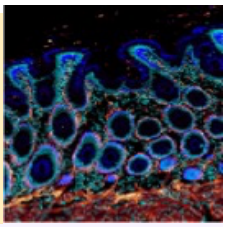
Example schematic of Dr. Bafor's research area:



Bafor EE, Valencia JC, Young HA.
Double Negative T Regulatory Cells: An Emerging Paradigm Shift in Reproductive Immune Tolerance?
doi: 10.3389/fimmu.2022.886645. PMID: 35844500; PMCID: PMC9283768.

Continued>>

IIG - FAES SYMPOSIA on BARRIER IMMUNITY
NOV 15-17, 2023
NIH-BETHESDA MD (NATCHER BUILDING)



WEDNESDAY, NOVEMBER 15

The Epithelial Barrier

Sunny Shin (U Penn)
De'Broski Herbert (U Penn)
Niki Moutsopoulos (NIDCR)
Short Talk from Abstracts

Inflammation and Myeloid Cells

Kate Fitzgerald (U Mass)
Renato Ostuni (Vita-Salute San Raffaele U)
John O' Shea (NIAMS)
Short Talk from Abstracts

Poster Session 1

Workshop 1

Short Talks from Abstracts

Adaptive Immunity at the Barrier

Lydia Lynch (Harvard)
Jenny Ting (UNC)
Michael Lenardo (NIAID)
Short Talk from Abstracts

THURSDAY, NOVEMBER 16

Pathobionts at the Barrier

Christina Stallings (Wash U)
Richard Maizels (U Edinburgh)
Yasmine Belkaid (NIAID)
Short Talk from Abstracts

Viral Immunity at the Barrier

Clive McKimmie (U Leeds)
Carolyn Coyne (Duke)
Gabriel Parra (FDA/CBER)
Short Talk from Abstracts

Poster Session 2

Workshop 2

Short Talks from Abstracts

Neuro-Immune Axis at the Barrier

Mauro Costa-Mattioli (BCM)
Gloria Choi (MIT)
Vanja Lazarevic (NCI)
Short Talk from Abstracts

FRIDAY, NOVEMBER 17

Systems Immunology at the Barrier

Sepideh Dolatshahi (U Virginia)
Smita Krishnaswamy (Yale)
Ron Germain (NIAID)
Short Talk from Abstracts

Tumor Immunity at the Barrier

Ming Li (MSKCC)
Edna Cukierman (Fox Chase)
Giorgio Trinchieri (NCI)
Short Talk from Abstracts

The IIG committee are excited to share the final flyer for the upcoming Barrier Immunity symposium that will take place in November 2023. Stay tuned for registration information!

Continued>>

Immunology Interest Group
SPOTLIGHT

Dr. Vanja Lazarevic is a Senior Investigator and Chief of Immunopathogenesis Section in the National Cancer Institute. To learn more about her work visit: https://ccr.cancer.gov/staff-directory/vanja-lazarevic

Tell us about your science.

Our laboratory investigates the intricate world of gene regulation and immune responses to gain insights into the mechanisms driving autoimmune inflammation. By focusing on transcription factors and their downstream targets, we aim to understand how dysregulated gene expression contributes to chronic inflammation and autoimmune diseases. Our interdisciplinary approach combines molecular and cellular immunology, biochemistry, genetics, and animal models to comprehensively investigate the impact of transcription factors on innate and adaptive immune cells. Our current focus is on unraveling the role of the transcription factors T-BET, RUNX1, and EGR2 in the development of organ-specific autoimmunity and mapping the transcription factor networks that drive the differentiation of pathogenic CD4+ T cells and innate lymphoid cells in the context of CNS autoimmune disorders. Ultimately, our goal is to unravel the molecular mechanisms underlying immune dysfunction and pave the way for targeted therapeutics for autoimmune conditions.

Vanja Lazarevic, Ph.D.

What event(s) lead to your career in science and interest in immunology?

The civil war in my home country of Bosnia and Herzegovina during 1992-1996 was a challenging time, and it was during this period that my journey into science and immunology took an unexpected turn. While working as an interpreter for the International Rescue Committee, I came across a Newsweek special edition reporting on the 1995 Ebola outbreak in Zaire, which ignited my fascination with infectious diseases and immunology.

How has a mentor or colleague substantially influenced your career trajectory?

I have had a great fortune to be mentored by four amazing scientists - Drs. Elizabeth Sockett, JoAnne Flynn, Laurie Glimcher and Yasmine Belkaid. Their tenacity, fearlessness, and passion for their work have been a constant source of inspiration and strength as I navigated the path towards independence in my own research pursuits.

In what area(s) do you expect significant research/medical advances in the next 5-10 years?

Predicting the next breakthrough in immunology is challenging, but several areas show promising potential for significant advances in the next 5-10 years, such as neonatal immunity, the aging of the immune system, neuroimmunology, immunoengineering, and the integration of artificial intelligence and mathematical modeling in immunology research. These areas highlight the importance of understanding immune responses at different stages of life, address age-related immune dysfunctions, harness engineering principles for immune-based therapies, and leverage cutting-edge technologies to enhance our understanding of immune processes.

What do you value most about the NIH-FDA Immunology community?

What I value most about the NIH-FDA IIG community is the collaborative and intellectually vibrant scientific environment it fosters. Interacting with friendly and exceptionally talented colleagues has been a source of inspiration and personal growth. I am particularly grateful to the NIH-FDA IIG committee for their exceptional work in organizing engaging seminar series, mini-symposia, and workshops, which further enhance the scientific community's cohesion and knowledge exchange. Their dedication and efforts have contributed significantly to the vibrant and stimulating atmosphere at NIH, making it an exceptional place for research and discovery.

How do you spend your free time?

Gardening, reading, traveling (tracking down forgotten and remote lighthouses).

Continued>>

Congratulations to the 2023 NIH-Penn Scholars!!!

To meet the demands of 21st century biomedical research, the National Institutes of Health (NIH) and the University of Pennsylvania (Penn) have committed to jointly training the next generation of immunologists. With the NIH-Penn Advanced Scholar in Immunology Graduate Partnership Program, this unique inter-campus collaboration provides access to graduate training for candidates admitted to the University of Pennsylvania Immunology Graduate Group (IGG). Combined with unparalleled access to research resources at both centers, this program features personalized mentorship from scientific leaders from both NIH and the University of Pennsylvania.

The mission of the program is to train immunologists who will push the boundaries of our understanding of the immune system and use that knowledge to make a tangible impact on human health and well-being, both today and for generations to come.

The new class is starting the academic year on August 15th, 2023, at the University of Pennsylvania and they will return to the NIH in spring of 2024 to conduct basic, translational, or clinical research within NIH intramural laboratories.

Meet our 2023 NIH-Penn Advanced Scholars!

Lutfi Huq graduated from Cornell University where he studied biology, mathematics, and computer science. He completed research internships at Stanford Medical School, Mayo Clinic, and NIH in the laboratories of Dr. Yasmine Belkaid and Dr. Steve Rosenberg. Lutfi is interested in tissue-resident T cells, their developmental pathways, and their use in novel cell-based treatments against cancer and infections.

Hannah Dobson graduated from the University of Rhode Island where she studied cell and molecular biology. Since then, she pursued research in fungal pathogenesis, cancer immunotherapy and autoimmune diseases. Hannah's scientific interests lie at the intersection of innate and adaptive immunity and immune dysregulation in infectious diseases, cancer, and autoimmunity.

Nathan Swanbery graduated from Colgate University where he studied molecular biology. As an undergraduate, Nate became fascinated with the developmental pathways of cutaneous γδ T cells and their role in peripheral immune responses. Nate's research interests center around T cell development, including their interactions with innate immune cells in the tumor microenvironment.

To learn more about our Scholars and the Program, please visit: https://www.med.upenn.edu/nih-igg-partnership/

Continued>>

Bench-to-Bedside in Action

Translating immunology to transform clinical care

Harnessing fundamental knowledge to advance our understanding of disease and develop novel treatment strategies is a major mission of the NIH. Each month we highlight interesting clinical trials taking place at the NIH Clinical Center that are doing just that.

Mediterranean-like Unprocessed (CLEAN-MED) Diet Intervention Study of the Gut Microbiome of Healthy Adults PI: Karen M. Frank, M.D., Ph.D., D(ABMM) – Chief, Department of Laboratory Medicine,

Background: This study (CLEAN-MED Diet Study) seeks to examine associations between the gut microbiome, well-being, and adherence to a Mediterranean-like unprocessed food diet. The premise of this study is based on the well-known health benefits of a healthy Mediterranean diet (MedDiet), rich in fiber and polyphenols, and the potential role that the gut microbiota may serve as a factor in health and disease. The MedDiet typically consists of high intake of vegetables, legumes, fruits, nuts, whole-grain cereals, fish, and olive oil, while limiting poultry, dairy, refined grains, red meats, and sweets. This study categorizes ultra-processed foods using the NOVA system. Ultra-processed foods, which contain high amounts of additives, are associated with reduced abundance of beneficial microbes and increased incidence of adverse health outcomes.

Hypothesis: Switching from a baseline Western diet to a strict Mediterranean-like and unprocessed food (CLEAN-MED) diet will result in significant changes in the gut microbiome.

Study Design: The study is actively recruiting healthy adults, who agree to adhere to a strict Mediterranean-like diet with unprocessed foods, meticulously log their food intake, while providing photographs of ingredient lists, share their perceived quality of life using provided questionnaires/tools, and collect periodic biological samples for analysis. The study consists of: (1) a short-term cohort who will complete a crossover study design with their habitual Western diet for 4 weeks and the intervention Mediterranean-like unprocessed food diet for 4 weeks (with CLEAN-MED diet food provided by the NIH metabolic kitchen), and (2) a long-term cohort who will continuously adhere to the Mediterranean-like unprocessed food diet for 12 months, following assessment of their baseline diet. Long-term study subjects participate in educational sessions with experienced dieticians. Additional objectives of the study, beyond examination of the gut microbiome, include identifying associations between CLEAN-MED diet adherence and psychosocial variables, such as perceived quality of life, identifying associations between changes in the gut microbiome and additional biomarkers, and measuring the level of adherence to the diet given a strict request for data submission and our methods of data submission.

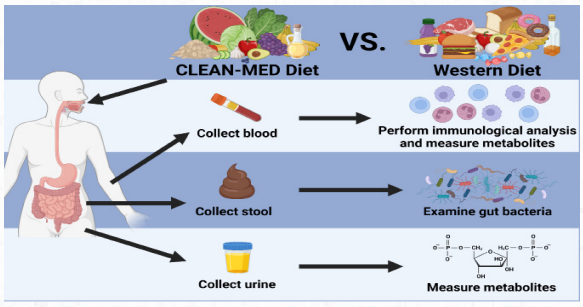


Fig 1. Overview of CLEAN-MED diet study biological specimen collection and analyses.

What we hope to learn: There are limited studies comparing the Mediterranean diet to ultra-processed foods, and even fewer with detailed gut microbiome data in association with this combination diet. The detailed ingredient analysis in this study will allow us better understand the role of dietary changes on gut microbiota and health from the lens of food-as-medicine.

Continued>>

Immunology Interest Group
SEMINAR SERIES

summer break

Kudos to IIG Committee members that successfully organized Immunology Interest Group Seminar Series 2022-2023

Alexandra O'Sick, Barrier Immunity Section, NIAID
Roxane Tussiwand, Immune Regulation Unit, NIDCR
Chuan Wu, Experimental Immunology Branch, NCI

Kudos to IIG Committee members that successfully organized Immunology Interest Group Fellows Lunch Series 2022-2023

Oyebola Oyesola, Type 2 Immunity Section, NIAID
Susannah Shissler, T-cell biology and development unit, NCI
Alexandria Wells, Meatorganism Immunity Section, NIAID
Amy Zhang, Immunoregulation Section, NEI

Missed a seminar?

Catch up on prior talks at...

https://www.niaid.nih.gov/research/immunology-seminars
FDA: http://web.microsoftstream.com/channel/5c371a75-2d56-45d3-9f86-7bacc3015066

*Recordings are generally available 1-2 weeks after the presentation.

Continued>>

Join the Listserv!
Immunology Interest Group

Share with new colleagues and trainees that join the lab:

Please visit the IIG website and (re)subscribe to the IMMUNI-L NIH Listserv with your NIH or FDA email address:

https://www.niaid.nih.gov/research/immunology-interest-group

You should recieve a quick confirmation of your subscription, and once you do, you should be able to post.

Please make note of the guidelines for the content that you post.

Sometimes there is a 30 minute delay in recognizing your email, but it is usually recognized quickly, and then you will be able to post.